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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 11/03/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/881,446	STAR ET AL.	
	Examin r	Art Unit	
	Gary W. Counts	1641	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-16 and 35-54* is/are pending in the application.

4a) Of the above claim(s) *45-54* is/are withdrawn from consideration.

5)☐ Claim(s) _ is/are allowed.

6)☒ Claim(s) *1-12,14-16 and 35-44* is/are rejected.

7)☐ Claim(s) _ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the claims

The Amendment filed August 19, 2003 is acknowledged and has been entered.

Election/Restrictions

1. Newly submitted claims 45-54 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 45-54 require selectively fluorescently labeling the cells or other tissue structures in the tissue sample for subsequent detection while reducing degradation of nucleic acid that occurs during more prolonged fluorescent staining.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 45-54 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-12, 14-16 and 35-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35, line 5 "other tissue structures" is vague and indefinite. It is unclear what applicant is referring to. There is no definition or guidance provided for the phrase in the specification.

Claim 36, line 3 "tissue structures" is vague and indefinite. It is unclear what applicant is referring to. There is no definition or guidance provided for the phrase in the specification. See deficiencies throughout the claims.

Claim 38, line 6 "other tissue structures" is vague and indefinite. It is unclear what applicant is referring to. There is no definition or guidance provided for the phrase in the specification. See also deficiency in claims 39 and 42.

Claim 43 is vague and indefinite because it is unclear how the specific binding agent is generated. It is unclear what relationship exits between the primary and secondary binding agents. Do they bind to each other or do both bind to another agent.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1, 35 and 39 are rejected under 35 U.S.C. 102(a) as being anticipated by Fink et al (Immunostaining and Laser-Assisted Cell Picking for mRNA analysis, Laboratory Investigation, March 2000, Vol 80, p. 327-333).

Fink et al disclose a method for fluorescently labeling tissue. Fink et al disclose incubating the tissue with a FITC-conjugated antibody (fluorescent specific binding

agent) for 3 to 10 minutes (p. 332). Fink et al also disclose the preservation of mRNA (biological molecule). Fink et al disclose identifying cells of the tissue and microdissecting the cells from the tissue.

With respect to the biological molecule in the issue is preserved after the tissue is contacted with the fluorescent specific binding agent, by labeling the cells or other tissue structures in less than five minutes as recited in the instant claims. Since Fink et al disclose using the same type of binding reagent and same time frame as the instantly recited claims one would expect the molecule to be preserve as recited by applicant. Therefore, the Fink et al reference encompasses the recited claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 4-6, 9, 35, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al (US 6,251,467) in view of Fink et al (Immunostaining and Laser-Assisted Cell Picking for mRNA Analysis, Laboratory Investigation, March 2000 Vol 80, p. 327-333).

Liotta et al disclose a method for microdissecting a tissue. Liotta et al disclose labeling molecules such as antibodies or fragments thereof (specific binding agent) which are directed to a specific cell or group of cells in the tissue sample. Liotta et al

disclose that this coupling of the labeled antibody to the tissue provides for imaging the tissue with a camera (col 4, lines 15-67). Liotta et al disclose microdissecting the cells from the tissue sample by applying a transfer film (capture member) on the tissue sample and applying laser energy to the cells (component of interest) to adhere the cells to the transfer film (col 11). Liotta et al also disclose that for mRNA analysis the tissue specimen can be placed on agarose and treated with agents to denature or otherwise inhibit Rnase (preserve mRNA) (col 8).

Liotta et al differ from the instant invention in failing to specifically teach that the label is fluorescent and that the fluorescent specific binding agent is directed in less than about five minutes.

Fink et al disclose a method for fluorescently labeling tissue. Fink et al disclose incubating the tissue with a FITC-conjugated antibody (fluorescent specific binding agent) for 3 to 10 minutes (p. 332). Fink et al also disclose the preservation of mRNA (biological molecule). Fink et al disclose identifying cells of the tissue and microdissecting the cells from the tissue. Fink et al disclose that the use of this immunofluorescence staining reduced the number of antibodies and incubation periods and thus provide more rapid protocols for immunofluorescence (abstract).

It would have been obvious to one of ordinary skill in the art to incorporate the use of a fluorescent label as taught by Fink et al into the method of Liotta et al because Fink et al shows that the use of this fluorescent label reduced the number of antibodies and incubation periods and thus provide more rapid protocols for immunofluorescence.

8. Claims 2, 3, 7, 8, 10, 11, 14-16, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al in view of Fink et al as applied to claims 1, 4-6, 9 and 35 above, and further in view of Rushbrooke et al (US 4,922,092).

See above for teachings of Liotta et al and Fink et al.

Liotta et al and Fink et al differ from the instant invention in failing to provide an intensified image signal and a filter.

Rushbrooke et al disclose the use of an image intensifier coupled with a camera. Rushbrooke et al also disclose that the image intensifier can include a filter. Rushbrooke et al disclose that this image intensifier increased the photon coupling between the sources and the intensifier and enhances the number of photons available for supply to the detector (col 7).

It would have been obvious to one of ordinary skill in the art to incorporate an image intensifier as taught by Rushbrooke et al into the modified method of Liotta et al because Rushbrooke et al shows that that this image intensifier increased the photon coupling between the sources and the intensifier and enhances the number of photons available for supply to the detector.

With respect to the sufficient concentration of the specific binding agent and the exposure time of the specific binding reagent to the tissue as recited in the instant claims, the optimum concentration and the optimum exposure time can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general

conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

9. Claims 1-11, 14-16, 35, 39, 40, 42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al in view of Fink et al and Rushbrooke et al.

Liotta et al disclose a method for microdissecting a tissue. Liotta et al disclose labeling molecules such as antibodies or fragments thereof (specific binding agent) which are directed to a specific cell or group of cells in the tissue sample. Liotta et al disclose that this coupling of the labeled antibody to the tissue provides for imaging the tissue with a camera (col 4, lines 15-67). Liotta et al disclose microdissecting the cells from the tissue sample by applying a transfer film (capture member) on the tissue sample and applying laser energy to the cells (component of interest) to adhere the cells to the transfer film (col 11). Liotta et al also disclose that for mRNA analysis the tissue specimen can be placed on agarose and treated with agents to denature or otherwise inhibit Rnase (preserve mRNA) (col 8).

Liotta et al differ from the instant invention in failing to specifically teach that the label is fluorescent and that the fluorescent specific binding agent is directed in less

than about five minutes. Liotta et al also differs from the instant invention in failing to provide an intensified image signal and a filter.

Fink et al disclose a method for fluorescently labeling tissue. Fink et al disclose incubating the tissue with a FITC-conjugated antibody (fluorescent specific binding agent) for 3 to 10 minutes (p. 332). Fink et al also disclose the preservation of mRNA (biological molecule). Fink et al disclose identifying cells of the tissue and microdissecting the cells from the tissue. Fink et al disclose that the use of this immunofluorescence staining reduced the number of antibodies and incubation periods and thus provide more rapid protocols for immunofluorescence (abstract).

Rushbrooke et al disclose the use of an image intensifier coupled with a camera. Rushbrooke et al also disclose that the image intensifier can include a filter. Rushbrooke et al disclose that this image intensifier increased the photon coupling between the sources and the intensifier and enhances the number of photons available for supply to the detector (col 7).

It would have been obvious to one of ordinary skill in the art to incorporate the use of a fluorescent label as taught by Fink et al into the method of Liotta et al because Fink et al shows that the use of this fluorescent label reduced the number of antibodies and incubation periods and thus provide more rapid protocols for immunofluorescence

It also would have been obvious to one of ordinary skill in the art to incorporate an image intensifier as taught by Rushbrooke et al into the modified method of Liotta et al because Rushbrooke et al shows that that this image intensifier increased the photon

coupling between the sources and the intensifier and enhances the number of photons available for supply to the detector.

Allowable Subject Matter

10. Claims 12 and 41 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

See previous office action for reasons for indication of allowable subject matter.

11. Claim 38 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

See previous office action for reasons for indication of allowable subject matter.

Response to Arguments

12. Applicant's arguments filed August 19, 2003 have been fully considered but they are not persuasive.

102 rejection arguments

Applicant argues that the Fink describes protocols for immunohistochemistry and immunofluorescene with total incubation times of approximately 25 to 40 minutes and 10 to 20 minutes. Applicant argues that the Fink method is one with a total incubation time of 10 to 20 minutes. Applicant argues that even assuming the wash step described by Fink was simultaneous, that the labeling procedure described by Fink on page 332 could take no less than 6 minutes. This is not found persuasive because the claims as recited only require that the fluorescent specific bind agent be directed in less than about five minutes. Fink et al clearly states on page 332 "incubation with the FITC-conjugated goat anti-mouse

immunoglobulin was performed for 3 to 10 minutes. Therefore, Fink teaches that the fluorescent specific binding agent (FITC-conjugated immunoglobulin) is directed in less than about 5 minutes and thus Fink et al reads on the instantly recited claims.

103 rejection arguments

Applicant argues that Fink et al does not make up for the deficiencies of Liotta and that Liotta and Fink do not teach or suggest all of the elements of the claims, and a *prima facie* case of obviousness has not been established. This is not found persuasive because of reasons stated above. Therefore, it is the Examiner's position that the combination of Liotta and Fink do teach all of the elements of the claims, and that a *prima facie* has been established.

Further, even if one were to consider total incubation time as applicant argues, the total incubation time can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

Applicant argues that Liotta and/or Fink do not teach or suggest "selectively label[ling] target cells... in less than about five minutes and that Rushbrooke does not teach or suggest this limitation. This is not found persuasive because as stated above it is the Examiner's position that the aforementioned references do teach this limitation and therefore the combination of Rushbrooke with the references is proper.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (703) 305-1444. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gary W. Counts
Examiner
Art Unit 1641
October 23, 2003

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
10/21/03